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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/565,673	08/10/90	VAN DER LAAN J	IH

HM12/0627
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EXAMINER	
FRONDA,C	
ART UNIT	PAPER NUMBER
1652	58

DATE MAILED: 06/27/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
07/565,673	Van Der Lann et al.
Examiner	**Group Art Unit**
Christian L. Fronda	1652

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *41-53* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *41-53* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claim Rejections - 35 U.S.C. § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 44, 49, and 51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The meaning of the phrase "or a derivative thereof said derivative retaining characteristics of the parent strain" is uncertain because the specification nor these claims recite the characteristics of the parent strain. Hence, claims 44, 49, and 51 fail to particularly point out and distinctly claim the subject matter of the invention.

Claim Rejections - 35 U.S.C. § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

4. Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fahnestock *et al.* in view of Aunstrup *et al.*

Fahnestock *et al.* teach methods for constructing a mutant Bacillus strain having low levels of extracellular protease by homologous recombination and a plasmid containing an integration cassette which is integrated into the genome of the Bacillus strain. Fahnestock *et al.* further teach that such strains are superior hosts for recombinant production of heterologous proteins such as Staphylococcal protein A and that higher levels of intact protein are obtained compared to previously available Bacillus strains (see entire publication). Fahnestock *et al* do not teach the method of claim 48. Aunstrup *et al.* teach extracellular proteases from alkalophilic Bacillus species (see abstract and entire publication)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an alkalophilic Bacillus strain according to claim 48 by modifying the teachings of Fahnestock *et al.* in the following manner: purify the extracellular proteases produced by the alkalophilic Bacillus strains taught by Aunstrup *et al.* by chromatography methods well known in the art; determine the amino acid sequence of the purified protease and construct DNA probes based on the amino acid sequence for use in screening libraries in order to obtain the gene by methods well known in the art; use the methods taught by Fahnestock *et al.* to mutate the gene and use the mutated gene for homologous recombination in an alkalophilic Bacillus strain taught by Aunstrup *et al.* in order to create a mutant alkalophilic Bacillus strain having reduced levels of extracellular high alkaline protease.

One of ordinary skill in the art would be motivated to make the alkalophilic Bacillus strain according to claims BB because mutated Bacillus strains are useful for recombinant production of heterologous proteins and higher levels of heterologous proteins are to be obtained as taught by Fahnestock *et al.*

5. Claims 41, 42, 45-47, 50, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fahnestock *et al.* in view of Aunstrup *et al.*, Hastrup *et al.*, and Dean *et al.*

Fahnestock *et al.* teach methods for constructing a mutant Bacillus strain having low levels of extracellular protease by homologous recombination and a plasmid containing an integration cassette which is integrated into the genome of the Bacillus strain. Fahnestock *et al.* further teach that such strains are superior hosts for recombinant production of heterologous proteins such as Staphylococcal protein A and that higher levels of intact protein are obtained compared to previously available Bacillus strains (see entire publication). Fahnestock *et al.* do not teach the method of claims 41, 42, 45 - 47 or the product of claims 50 and 52. Aunstrup *et al.* teach extracellular proteases from alkalophilic Bacillus species (see abstract and entire publication). Dean *et al.* teach methods for creating an asporogenic Bacillus sp. mutant (see

entire US 4,450,235). Hastrup *et al.* teach that secretion of proteases in Bacillus sp. is linked to the bacterial growth cycle, with greatest expression of protease during the stationary phase, when sporulation also occurs (see entire WO 89/06279; and p.3, lines 15-27). Inherently, production of proteases during sporulation would reduce the levels of recombinant heterologous proteins expressed in Bacillus sp. since these proteases would degrade the recombinant proteins.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an alkalophilic Bacillus strain according to claims 50 and 52 for use in making a mutant high alkaline protease of claims 41, 42, 45 - 47 by modifying the teachings of Fahnestock *et al.* in the following manner: obtain the gene encoding any one of the high alkaline proteases taught by Aunstrup *et al.* by purifying the selected protease by chromatography methods, obtaining the amino acid sequence of the purified protease, constructing DNA probes based on the amino acid sequence, and screening libraries with the DNA probes for the gene encoding the selected protease; mutate the gene by random mutagenesis (i.e., treatment with UV irradiation or mutagenic chemical agents) or site-directed mutagenesis; transform the mutated gene into the Bacillus strain stated above in the rejection of claim 48 by the homologous recombination method taught by Fahnestock *et al.*; and express, purify, and isolate the mutated protease having the desired properties (such as increased enzyme activity) from the host cell by chromatography methods which are well known in the art. One of ordinary skill in the art would be motivated to do this because mutated Bacillus strains having reduced protease levels are useful for recombinant production of mutant high alkaline protease and higher levels of mutant high alkaline protease are to be obtained as taught by Fahnestock *et al.*

Furthermore, It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an asporogenic Bacillus strain according to claims 43 and 53 by further modifying the modified method of Fahnestock *et al.* which is stated in the previous paragraph in the following manner: using the methods of Dean *et al.* create an asporogenic alkalophlilic host Bacillus strain from any parental alkalophilic Bacillus strain taught by Aunstrup *et al.* and use this mutant asporogenic alkalophilic Bacillus strain as a host which is to be transformed with the mutated gene for high alkaline protease. One of ordinary skill in the art would be motivated to do this because Hastrup *et al.* teach that greatest expression of proteases occur during sporulation in a wild type Bacillus sp., and inherently an asporogenic Bacillus sp. is expected to be suitable for high expression levels of intact heterologous proteins since such great level of protease expression which would degrade the recombinant protein would not occur in the asporogenic Bacillus sp.

Conclusion

6.. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L. Fronda whose telephone number is (703)305-1252. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703)308-3804. The fax phone number for this Group is (703)308-0294. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703)308-0196.

CLF
June 9, 2000

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